PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference ON/4-33222A/USN	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/EP2004/006070	International filing date *(day/month/year)* 04.06.2004	Priority date *(day/month/year)* 06.06.2003
International Patent Classification (IPC) or national classification and IPC A61K31/404, A61P7/00, A61P11/00, A61P43/00		
Applicant NOVARTIS AG		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
17.12.2004	09.08.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Taylor, G.M. Telephone No. +49 89 2399-

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/006070

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-43 as originally filed

   Claims, Numbers

   1-21 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-5,8-10,12-21

because:

☒ the said international application, or the said claims Nos. 1-5,8-10,13-21 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1-5,8,10,12,13,19,20,21 are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-5,8-10,12-21

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/006070

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-21
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-21
Industrial applicability (IA)	Yes:	Claims	1-7,10-12
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Section III

1. Claims 1-5, 8, 10, 12, 13 and 19-21 were only searched in as far as the treatment of hypereosinophilic syndrome is concerned. This opinion will also be restricted to such subject-matter (Rule 66.1(e) PCT).

2. Claims 8, 9 and 13-21 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Art. 34(4)(a)(I) PCT).

Section V

D1: EP-A-0 296 110 (CIBA GEIGY AG) 21 December 1988 (1988-12-21)
D2: EP-A-0 657 164 (CIBA GEIGY AG) 14 June 1995 (1995-06-14)
D3: COOLS, J. ET AL.: "PKC412 overcomes resistance to imatinab in a murine model of FIP1L1-PDGFRa-induced myoproliferative disease" CANCER CELL, vol. 3, 19 May 2003 (2003-05-19), pages 459-469, XP002302132

3. The claimed subject-matter is not novel in view of the disclosures of D1-D3 (Art. 33(2) PCT); see the passages cited in the search report.

3.1 In particular, D3 discloses that PKC412, a.k.a. Midostaurin (cf. present description, page 35, paragraph 4; claims 10, 12, 13, 19) is effective *in vivo* in overcoming resistance to imanitab in a murine model of FIP1L1-PDGFRα-induced myeloproliferative diseases.

3.2 Notwithstanding the objections made in view of D3, the claims to products and first medical uses (claims 12 and 19) also lack novelty because Midostaurin was already known as a medicament at the claimed priority date.

4. There would not appear to be any novel subject-matter in the present set of claims which could be considered as being inventive (Art. 33(3) PCT).

Section VI

5. The following documents are cited under Rules 64.3 and 70.10 PCT:

KILON, A.D. ET AL.: "Elevated serum tryptase levels identify a subset of patients with a myeloproliferative variant of idiopathic hypereosinophilic syndrome

associated with tissue fibrosis, poor prognosis and imatinab responsiveness" BLOOD, vol. 101, no. 12, 3 April 2003 (2003-04-03), pages 4660-4666, XP002302133.

COOLS J ET AL: "THE EOL-1 CELL LINE AS AN IN VITRO MODEL FOR THE STUDY OF FIP1L1-PDGFRA POSITIVE CHRONIC EOSINOPHILIC LEUKEMIA" BLOOD, W.B.SAUNDERS COMPAGNY, ORLANDO, FL, US, vol. 102, no. 11, 16 November 2003 (2003-11-16), page 593A, XP001194818 ISSN: 0006-4971.

COOLS J, ET AL.: "The EOL-1 cell line as an in vitro model for the study of FIP1L1-PDGFRA-positive chronic eosinophilic leukaemia" BLOOD, vol. 103, no. 7, 1 April 2004 (2004-04-01), pages 2802-2805, XP002302134.

COOLS, J. ET AL.: "CHIC2 deletion, a surrogate for FIP1L1-PDGFRA fusion, occurs in mastocytosis associated with eosinophilia and predicts response to imatinib mesylate therapy" BLOOD, vol. 102, no. 9, 1 November 2003 (2003-11-01), pages 3093-3096, XP002302135.

COOLS, J. ET AL.: "The FIP1L1-PDGFRa kinase in hypereosinophiic syndrome and chronic oesinophilic leukaemia" CURR. OPIN. HEMATOL., vol. 11, January 2004 (2004-01), pages 51-57, XP002302136.

Section VIII

6. The objections raised in the search report to the clarity of claims 1-5, 8, 10, 12, 13 and 19-21 is upheld (Art. 6 PCT).

7. The expressions "lower alkyl", "lower alkoxy" etc. are unclear because there is no generally accepted interpretation for the maximum number of carbon atoms which the definition "lower" is intended to encompass.

8. Claim 15 is unclear because claims 10-12 do not relate to methods.

9. The category of claim 20 is unclear because the applicant is attempting to claim an article of manufacture in terms of its method of use.